

M.I.R.I.A.D. Biobank

Material and Information Resources for Inflammatory and Digestive Diseases

A newsletter about research at Cedars-Sinai IBD

MIRIAD Participation Leads to a New Drug for IBD, Now Being Tested in Clinical Trials

by Janine Bilsborough, PhD, Director, Cedars-Sinai IBD Drug Discovery and Development Unit

Have you ever wondered whether participating in the MIRIAD Biobank makes any difference? The ultimate goal of all physician/scientists is to make a difference for patients. We do that by learning more about the causes of disease and using that knowledge to discover and develop new treatments. This process typically takes a long time and that is especially true for complicated diseases such as Crohn's disease and ulcerative colitis. Physicians/scientists who advocate for much-needed new therapies are key to making sure new treatment options become available for patients.

We are proud to say that Cedars-Sinai IBD scientists and physicians, in partnership with hundreds of MIRIAD Biobank participants, have worked hard to understand the role of a molecule known as TL1A in IBD. In December 2020, as a result of this body of work and the commitment we have to impacting patient lives, the FDA authorized Prometheus Biosciences, a spinoff of Cedars-Sinai IBD, to begin clinical testing of a new IBD drug that blocks the effect of TL1A. More importantly, Cedars-Sinai IBD scientists have developed a way to identify patients who are likely to benefit from this new treatment. It's a huge step toward "giving the right treatment to the right patient at the right time and in the right way," as Stephan Targan, Cedars-Sinai IBD director, likes to say. This approach of using information to predict which patients will benefit from certain treatments can result in much better responses to newly discovered therapies. So, yes, participating in the MIRIAD Biobank makes a difference!

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IBD Surgery Research Is on the Cutting Edge at Cedars-Sinai IBD

by Phillip R. Fleshner, MD, Director, IBD Surgery Research and the Shirley, Jesslyne, and Emmeline Widjaja Chair in Colorectal Surgery

The IBD Surgery Research Program is unique in its direct integration with ongoing basic science, translational and clinical research efforts at Cedars-Sinai IBD. The combined focus advances the understanding to improve surgery and medical outcomes and at the same time extends the knowledge about the causes of IBD and the factors that distinguish one person's IBD from another's.

Medical treatment for IBD has two main goals: 1) achieving remission and 2) maintaining remission. Before 1998, physicians had only three types of drugs to use to try and achieve these goals, namely aminosalicylates, immunomodulators and steroids. Biologic therapy, introduced in 1998, involves molecules created in the laboratory that offer a distinct advantage in IBD treatment because their mechanisms of action are more precisely targeted to factors responsible for IBD, rather than global suppression of the immune system. The ability of biologic drugs to achieve and maintain remission has revolutionized the treatment of IBD patients.

Biologic drugs can have side effects, but the advantages far outweigh their risks. Because biologics interfere with important processes of wound healing, concerns have been expressed about the effects of these drugs in IBD patients who require surgery. Shortly after introduction of infliximab (Remicade™) in 1998, several studies demonstrated a higher risk of infection after surgery in patients with Crohn's disease and ulcerative colitis. These reports were followed by other studies that showed little if any effect of biologic drugs on postoperative outcomes. Many factors accounted for the differences in the findings, but varying time periods between the last biologic dose and surgery was a critical factor.

Investigators at Cedars-Sinai IBD endeavored to clarify the question of whether and how biologic therapy affected surgical outcomes. First, we knew that the most accurate measure of biologic drug effect in the IBD patient was the level of biologic medication in the blood. Second, thanks to the participation of MIRIAD IBD Biobank participants who agreed to have blood drawn for research at the time of surgery, samples were available to measure the level of the biologic. Lastly, these same MIRIAD Biobank participants agreed to allow collection of highly detailed information about their surgical outcomes. Taken together, these three factors allowed Cedars-Sinai IBD surgery researchers to show for the first time an association between blood level of anti-TNF drugs, such as Remicade™ (infliximab) and Humira™ (adalimumab) and surgical outcomes in ulcerative colitis, but not Crohn's disease.

Cedars-Sinai IBD surgeon-scientists extended their work to determine whether two other classes of biological drugs had an impact on surgical outcomes. The first report showed no adverse effect of the anti-integrin drug Entyvio™ (vedolizumab) and surgical healing. The second report, recently presented at the largest meeting of gastroenterology and colorectal surgery researchers, also showed no adverse effects of ustekinumab (Stelara™) and surgical outcomes.

These projects illustrate two things: 1) Cedars-Sinai IBD researchers are committed to understanding every aspect of IBD with a mind to optimizing treatment plans one patient at a time, and 2) the unique IBD Surgery Research Program is blazing trails by combining state-of-the-art research approaches with a unique perspective on surgery, which together improve surgical outcomes and patient lives.

Q&A With Gil Melmed, MD, About COVID-19 Vaccines and People With IBD

Melmed is the director of Clinical Trials and Clinical Research at Cedars-Sinai IBD and an expert on vaccines.

Q: Could the COVID-19 vaccine cause an IBD flare-up?

A: A number of studies of vaccines for influenza, pneumonia, shingles and others have been done in IBD and other chronic immune-mediated conditions. Those studies suggest no increased risk of a flare-up, and specifically, none of the IBD studies have shown increased risk of an IBD flare-up. These vaccines are new and different, so we're learning as much as we can, as quickly as we can, from real-world experience.

Q: Is it safe to take the vaccine while on immunomodulators or biologics?

A: Yes. What we know so far from emerging evidence from COVID-19 mRNA vaccines, and a wealth of evidence from other vaccines, we recommend patients receive COVID-19 vaccination irrespective of being on immunomodulators or biologics.

Q: Should I stop taking my IBD medication before getting the COVID-19 vaccine?

A: No. Based on experience with other vaccines, we recommend that our patients with IBD stay on their medication at the time of vaccination. An international panel of IBD experts endorses this approach, and recommends getting vaccinated at the earliest opportunity to do so.

Q: Is one vaccine better than another if I take IBD medications?

A: It's hard to specifically answer this question because people with IBD on immunosuppressant medications were not included in the trials. The two mRNA vaccines and the J&J vaccine all appear to be exceedingly safe and extremely effective, and we are not aware of any meaningful differences between them. We will learn more about this through our CORALE-IBD vaccine registry.

Q: What are scientists doing to get data on vaccine safety for people with IBD?

A: Cedars-Sinai and other institutions worldwide have launched registries for patients, and we are asking this exact question. Using scientific ways of looking at immunity, we're learning what happens after receiving a vaccine, e.g., how long immunity lasts, the quality of immunity over time and the nature of any side effects. To learn more about the CORALE-IBD registry, please visit corale-study.org/ibd.

Q: Will the vaccine side effects be more severe for people with IBD?

A: Our CORALE-IBD vaccine registry will hopefully give us an indication as to whether side effects in people with IBD are any different. In the populations that have been studied—including people with various compromising health conditions—side effects are usually mild and self-limited. Some GI side effects have been reported, such as nausea, vomiting or diarrhea. A question could arise as to whether those symptoms are vaccine side effects or a flare-up of IBD. Thus far, there have been no published reports of a true IBD flare-up related to COVID-19 vaccination.

Q: As someone with IBD, is there anything else I should know about the COVID-19 vaccine?

A: While we don't know all the answers about the safety and effectiveness of vaccines in the IBD population, we do know the risks of COVID-19. It's very important in any discussion of risks and benefits that we not just focus on the risks of a vaccine. The risk of getting COVID-19 is very real and it behooves anybody who is concerned to weigh the risks of getting a vaccine against the risks of getting COVID-19.

Adapted from an article by Sarah Ellis with Permission from HealthCentral (healthcentral.com/article/should-you-get-the-covid-vaccine-if-you-have-ibd)

IBD COVID-19 Vaccine Research Study (CORALE-IBD Study)

by Jonathan G. Braun, MD, PhD, Director, IBD Enterprise Operations

COVID-19, the disease resulting from infection with SARS-CoV-2, has reached nearly 100 million people globally, and 2 million have lost their lives. Vaccines to prevent COVID-19 are now available and are highly effective and safe in individuals without immune-mediated diseases. However, these vaccines have not yet been assessed in people with inflammatory bowel disease (IBD), who are commonly on immunosuppressant medications. Cedars-Sinai IBD scientists previously demonstrated that antibody responses to common vaccines can be reduced in people with IBD being treated with immunomodulators and certain biologics. A team led by Gil Melmed, MD, has begun CORALE-IBD, a study of vaccine responses in patients with IBD, to identify predictors of effectiveness and short- and long-term safety.

This study will have a direct clinical impact for patients with IBD and other immune-mediated diseases

You are eligible to participate in this study if you are scheduled to receive or recently received a COVID-19 vaccine. Participation in this study is being offered in particular to patients who have previously participated in our MIRIAD Biobank. You may be offered the opportunity to participate by a message in your My CS-Link Patient Portal, by mail or at in-clinic visits. Patients who have not yet participated in MIRIAD studies may also join, and we are offering a remote mode of participation for patients who reside elsewhere in the U.S.

plan, MIRIAD staff will collect clinical information, blood samples, stool and saliva. Follow-up blood samples will be collected at 8, 16, 24 and 52 weeks.

CORALE-IBD study participants will be able to choose the type and number of samples and surveys they will contribute to. In the fullest

Samples will be tested for level of antibodies to the vaccine. The CORALE team will compare IBD vs. healthy controls, IBD patients who by their treatment are immunosuppressed or non-immunosuppressed, and IBD vs. other immunocompromised patients. We will analyze therapeutic drug levels, disease activity and biochemical cellular markers of immune function, to identify factors that explain differences in the vaccine response. And, we will track antibody and other measures over time to assess durability of the vaccine response.

This study will have a direct clinical impact for patients with IBD and other immune-mediated diseases, as they will inform optimal SARS-CoV-2 vaccine selection, dosing and length of effectiveness. Data generated from this study will substantially expand MIRIAD as the largest and most comprehensive resource to advance understanding of the pathogenesis and natural history of IBD, and strategies for its treatment and prevention.

If you are interested in participating, contact us at corale-study.org/ibd. We are pleased that participating patients will receive back their own SARS-CoV-2 antibody levels.



IBD COVID VACCINE REGISTRY



www.corale-study.org/ibd

Phone: 310-423-5643
Email: ibdresearch@cshs.org

Scan with your smartphone for more information.



Comprehensive Care for Kids With IBD: The Pediatric IBD Program

by Shervin Rabizadeh, MD, MBA

The Cedars-Sinai Pediatric Inflammatory Bowel Disease Program is one of the largest in the country and specializes in the specific issues affecting children and teenagers with Crohn's disease and ulcerative colitis. IBD can occur at any age and our program was built around the premise of providing comprehensive care and support for young people with IBD. Therefore, the program is staffed by two physicians (Rabizadeh and David Ziring, MD), a nurse practitioner (Morgan Check), a dietitian (Erin Feldman), a social worker (Amy Mann) and a responsive, excellent administrative team (Shonya Coleman and Erika Lopez), covering the spectrum of the pediatric IBD experience. A unique feature of our program is an incorporated infusion center staffed by outstanding nurses, Sharmayne Farior and Chrissy Helbock, who are specially trained in pediatric IBD.

During the COVID-19 pandemic, the clinic has stayed open for patient visits and infusions, with virtual visits as an option for all patients, whether they are local or live far away.

During the COVID-19 pandemic, the clinic has stayed open for patient visits and infusions, with virtual visits as an option for all patients, whether they are local or live far away.

Mission critical for the program is advancing IBD research. Exceptional research clinical coordinators (Yvette Gonzales, Janet Perkins and Yogesh Arora) help the physicians perform cutting-edge work that includes clinical trials, multicenter pediatric IBD research projects and investigator-initiated projects. A very active pediatric IBD translational research effort is fully integrated with adult-based investigators.

Investigators deploy pharmacokinetics (the study of the way drugs move through the body) and multi-omics (the combination of data from various analytical approaches) to optimize drug therapies in pediatric IBD, and to study new treatment possibilities such as autologous stem cell treatment for severe refractory Crohn's disease. The team specializes in studying unique subgroups of pediatric IBD patients, such as those with very early onset IBD (patients diagnosed less than 6 years of age).

Other research involvement includes working with the pharmaceutical industry in performing clinical trials of new medications for pediatric IBD and by being a founding and participating site of multicenter pediatric IBD research initiatives that are making headway in understanding the contributing factors to IBD in children.

The MIRIAD Biobank aids pediatric IBD research by providing the infrastructure needed for not only obtaining and maintaining data and samples, but also facilitating collaborations, especially between clinicians and scientists. None of this research would be feasible without the generous commitment and willingness of patients and families to become MIRIAD Biobank participants.

Navigating Nutrition and IBD

by Kelly Issokson, MS, RD

Many people with IBD believe diet plays an important role in their treatment. Diet, or the foods we eat, can help us achieve and maintain nutrition balance, which is important for improving response to medical and surgical therapies that are often used to treat IBD. For some, active disease, symptoms or treatment options can make it difficult to eat and can lead to malnutrition. Recent research shows that people often make diet changes after being diagnosed with

IBD to help control symptoms or reduce the risk of worsening a flare-up. Some of those changes may lead to avoiding foods that help keep us healthy and happy.

A registered dietitian is an important member of your care team who can help guide you in testing foods and reintroducing foods back into your diet safely.

Studies on the role of diet, including specific diets that can help people with IBD, are growing. We know more about specific diet components and how they may affect symptoms and disease activity. One important finding from recent studies is that people with IBD who incorporate fiber (like fruits and vegetables) into their diet tend to have less symptoms and fewer disease flares over time. Nevertheless, incorporating fiber can be a challenge for people who have historically been told to avoid fiber, who were never guided on how or when to expand their diet, and/or had negative experiences with fiber-rich diets in the past.

A registered dietitian is an important member of your care team who can help guide you in testing foods and reintroducing foods back into your diet safely. Participants in the MIRIAD Biobank have supported nutrition research that has helped us understand diet beliefs, food avoidances and nutrient deficiencies in people with IBD, and are currently supporting research that will help us understand more about the role of nutrition therapy in patients with IBD who need surgery. As an IBD-focused dietitian at Cedars-Sinai IBD, I help translate the latest research for patients so they can confidently make informed decisions about how to adjust their diet to meet their health goals.



Integrative Medicine for IBD, Part 2: Complementary Therapy Considerations

by Eric Vasiliauskas, MD, Director, Cedars-Sinai Nutrition and Integrative IBD Program

(Note: In the next MIRIAD Biobank Newsletter, we will focus on herbal therapy.)

Both patients and medical providers are showing increased interest in understanding and defining the potential role of complementary and alternative medicine (CAM) therapies in the management of IBD.

The unfortunate reality is there is very little high-quality data on the safety and effectiveness of CAM in IBD.

When considering any therapy, it is important to weigh both risks and benefits. The unfortunate reality is there is very little high-quality data on the safety and effectiveness of CAM in IBD. While standard medical therapies go through a lengthy and rigorous process to determine safety and effectiveness, CAM therapies are generally not subject to the same careful evaluations. Too often, patients make decisions about CAM therapies based on anecdotal evidence, personal testimony, case reports or studies that include small numbers of patients.

Multiple issues complicate good decision-making about CAM. Compared to medications such as steroids and biologics, CAM therapies can take much longer to demonstrate their full potential benefits. Meanwhile, most studies have been too short term, study too

few patients, lack placebo controls and often don't thoroughly consider important background factors of the study group(s). Key endpoints such as response and remission are often not well-defined, nor as vigorous as expected by academic medical publications. Response is often loosely defined by a few specific symptoms or a sense of feeling better, but without more objective assessments combining symptom improvement with blood and stool tests of inflammation, and importantly, healing of the intestinal lining as assessed by endoscopy. The reality is that the quality of most CAM studies in IBD has been suboptimal.

Product considerations are also important. Very often the specific herb(s), fish oil, probiotic or other therapy studied is not commercially available, or readily accessible. Formulation can vary and also come with different side effects. For example, raw turmeric powder is high in oxalates, which can lead to kidney stones, whereas the purified extract is not. Many herbs can interact with medications. Individuals who are pregnant or contemplating pregnancy need to make sure therapies are safe in that setting.



While good information on herbal supplements can be found on the internet, the available information may be incomplete or not applicable in the context of an individual's specific situation. There is also a lot of bad information, misinformation and hype as well. The website "Herbs at a Glance," sponsored by the National Institutes of Health's National Center for Complementary and Integrative Health (NCCIH) is a good starting place to search for up-to-date, unbiased information, as well as links to research articles on various herbs.

Some interventions may work quickly, others take much longer to kick in. Thus, while some interventions may be used to quiet down specific symptoms or a flare-up, others may have the best chance of working once the inflammation has been quieted down with medication or surgery, as part of a longer-term maintenance strategy, or to prevent symptom or disease recurrence after surgery when many patients start with a "clean slate."

The key to many interventions, particularly long-term approaches, is compliance. Compliance can be challenging with complex regimens, multiple supplements and restrictive diets, especially if they will be used over time. There is a tendency, especially once feeling better or well, to be less stringent

Compared to medications such as steroids and biologics, CAM therapies can take much longer to demonstrate their full potential benefits.



in adherence to recommendations. Lack of compliance is one of the most common reasons patients with IBD experience disease flares. Importantly, symptoms may not return immediately after ceasing the intervention; they may start weeks to months after stopping a therapy.

Good integrative IBD care depends on a comprehensive approach that combines best of clinical, genetic and basic science research with decades of IBD-focused clinical experience.

MIRIAD Biobank Team Spotlight:

Phillip Fleshner, MD, Janine Bilsborough, PhD, and Research Coordinator Jennifer Davis.



Phillip Fleshner, MD

Shierley, Jesslyne, and Emmeline Widjaja Chair in Colorectal Surgery
Director, Colorectal Surgery Research

Fleshner has been engaged in the study of colorectal surgery for nearly 30 years and has been treating patients with colorectal disease surgically for the same period of time. World-renowned for his game-changing approach to surgery and to surgery research, he was recently elected to the prestigious International Organization for Inflammatory Bowel Disease. Fleshner's research is aimed at stratification of Crohn's disease and ulcerative colitis into subgroups based on the underlying genetic, environmental and biologic causes of disease and relating these to surgical outcomes. He uses the results to shape pre-op and post-op protocols. Fleshner is an avid hockey fan and enjoys going to Los Angeles Kings games.



Janine Bilsborough, PhD

Director, IBD Drug Discovery and Development Unit

Bilsborough is an immunologist who, prior to joining Cedars-Sinai IBD 10 years ago, worked in the biotech/pharma industry for 20 years and is intimately aware of the struggles to develop new therapies for autoimmune and inflammatory diseases. She is excited by the prospect of developing new therapies to improve quality of life in patients and is dedicated to the continual discovery of new therapeutic options for difficult-to-treat diseases. Bilsborough loves to spend time working with animals and relaxes through painting.



Jennifer Davis

Clinical Research Coordinator II

Jennifer Davis earned her bachelor's degree in health promotion and education from Weber State University in Ogden, Utah. She obtained public health experience working for the Utah State Health Department. Davis was involved in an epidemiological study to better understand a steep increase in sexually transmitted disease cases among high-risk groups. She has worked previously as a phlebotomist, where she enjoyed patient interaction. Davis joined the Cedars-Sinai F. Widjaja Inflammatory Bowel and Immunobiology Research Institute in January 2019. She currently works as part of the clinical research coordinator team in the MIRIAD group.

Important Numbers and Contact Information

- **Adult Patient Care Appointments:**
310-423-4100
cedars-sinai.org/programs/digestive-liver-diseases/clinical/ibd-center.html
- **Pediatric Patient Care Appointments:**
310-423 -7100
cedars-sinai.org/programs/digestive-liver-diseases/clinical/ibd-center/pediatric.html
- **IBD Clinical Trials Information:**
310-423-2041
cedars-sinai.org/programs/digestive-liver-diseases/clinical/ibd-center/clinical-trials.html
- **MIRIAD IBD Biobank**
310-423-3550
miriad.ibdbiobank@cshs.org
cedars-sinai.org/research/departments-institutes/ibiri/miriad-ibd-biobank.html